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GENERAL REVIEW

The next psychoactive drugs: From imipramine to ketamine



Psychotropes du futur: de l'imipramine à la kétamine

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Abstract Since the 1950s, the therapeutic arsenal against depression has grown considerably. From the discovery of mono-amine oxidase inhibitors (MAOIs) to the antidepressant effect of ketamine, several pharmacological breakthroughs made the history of psychiatry. These discoveries oriented the research about the pathophysiology of depression, which is one of the most disabling diseases worldwide affecting 10 to 20% of general population. In this article, we offer a short historical review of the various therapeutic options developed over the past century and the consequences of these innovations. We then review the discovery of the antidepressant effects of ketamine (and its S-enantiomer, esketamine), the lastest development in depression treatment. Ketamine's effects are spectacular both in terms of their very short onset time, and because they are observed even in treatment-resistant depression. Just as MAOIs and tricyclic antidepressants allowed the "monoaminergic hypothesis of depression" to emerge, unravelling the mechanisms of ketamine's antidepressant effects should highlight the role of glutamatergic system and neuro-inflammation in the neurobiology of depression. Ketamine might also help to refine our understanding of the cognitive pathophysiology of depression and to deeply transform the clinical representations of depressive disorder.

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MOTS CLÉS

Psychiatrie ;
Dépression ;

Résumé Depuis les années 1950, l'arsenal thérapeutique permettant de lutter contre la dépression s'est considérablement enrichi. De la découverte des inhibiteurs de la mono-amine oxydase (IMAO) à celle de la kétamine, ces percées pharmacologiques ont marqué l'histoire de la psychiatrie et guidé la recherche sur la physiopathologie de la dépression, cette pathologie

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dévastatrice affectant entre 10 et 20 % de la population mondiale. Nous proposons dans cet article une courte revue historique des différentes options thérapeutiques développées au cours du siècle passé et des conséquences qu'ont eues ces innovations. Nous réalisons ensuite un état des lieux de la plus récente de ces découvertes, celle des effets antidépresseurs de la kétamine (et de son énantiomère S, l'eskétamine), spectaculaires de par leur délai d'action et leur efficacité même dans les formes les plus résistantes de dépression. De même que la découverte des IMAO et des tricycliques a permis de concevoir une théorie monoaminergique de la dépression, l'étude des mécanismes d'actions de la kétamine pourrait permettre de comprendre le rôle de la transmission glutamatergique ou de la neuro-inflammation dans la neurobiologie de cette pathologie, d'affiner nos connaissances sur sa physiopathologie cognitive, ou encore de transformer en profondeur les représentations des cliniciens sur cette maladie.

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Depression is one of the most devastating illnesses in terms of human suffering, disability and cost to society across all medical specialties. It is estimated that 19% of French people aged 15 to 75 have experienced, are experiencing or will experience depression during their lifetime; suicide is the second leading cause of death among 15–29 year olds and depression is the leading cause of disability in the world according to the WHO [1]. Nowadays the pharmacological treatment of depression is essentially based on molecules targeting monoamines (serotonin, norepinephrine and dopamine) and in particular on selective serotonin reuptake inhibitors (SSRIs). However, resistance to antidepressants is a frequent phenomenon. It is estimated that after four lines of treatment, one in three depressed patients is in a situation of therapeutic failure [2]. The search for new strategies and new psychotropic drugs is therefore a major challenge, the discovery of the antidepressant effects of ketamine being without a doubt the most promising pharmacological avenue to date.

Historical perspective and serendipity

The discovery of the first antidepressant treatment dates to the 1950s. Prior to this date, the main pharmacological treatment for depression was opium. The use of the poppy was first described about 3400 BC in Mesopotamia, under the name 'Hul Gil' or plant of joy [3]. Opium and its derivatives such as opium tincture, whose "recipe" was proposed by the Swiss physician Paracelsus (1493–1541) and later improved and popularized by Sydenham [1624–1689], were widely used in depression. Hippocrates and then Galien described its use; Thomas de Quincey (1785–1859), the author of "Confessions of an English Opium-Eater", began using it to relieve depressive symptoms, and Kraepelin formally described in 1905 the use of opium in the treatment of depression [4]. Opium was administered daily with a gradual increase in dosage and a duration of two months for a cure -the possible addictive consequences of this type of cure being easily predictable.

As it frequently occurs in the history of medicine, it is a story of chance, favoured by minds well prepared by their clinical acuity, which will revolutionise the treatment of depression [5]. Indeed, the properties of the first two classes of antidepressant treatments, mono-amine oxidase

inhibitors (MAOIs) and tricyclics, were discovered by chance. Concerning MAOIs, it was at the Sea View Hospital in New York in 1952 that Selikoff and Robitzek first described that iproniazid, used as an antituberculosis drug, had as a "side effect" described as a "greater stimulation of the central nervous system". This was not observed with other related molecules such as isoniazid. Some patients had "increased vitality" and wanted to leave the hospital or were found dancing in the hallways despite their lung damage. Smith and Kamman saw this side effect as a benefit for their patients and described the euphoric, mood elevating effects of the molecule [6,7]. The first evaluation of the effects of iproniazid in depressed patients without tuberculosis was made in 1957 by Kline, a psychiatrist at the Rockland State Hospital in New York State [8]. As for tricyclics, their discovery originated in the characterization of the neuroleptic effects of chlorpromazine by Jean Delay and Pierre Deniker, which leads to the exploration of the effects of other substances pharmacologically close to this phenothiazine in psychiatry. The agent G-22355, the future imipramine, was first developed as an anti-histaminic agent [5]. The test of this substance in 1956 in patients suffering from schizophrenia was a failure, even inducing states of agitation in some patients (as of today, tricyclics are not recommended as first-line treatment for depression occurring in psychotic patients because of a delirious relapse risk). Roland Kuhn, however, observed in three patients with psychotic depression a clear improvement in their general state within a few weeks. He mentioned the possibility of antidepressant effects specific to this molecule, which was later confirmed, leading to the marketing of imipramine in 1957 [9].

Beyond their clinical efficacy, the discovery of MAOIs and tricyclics was a giant step forward in the understanding of the pathophysiology of depression. If these molecules were discovered by serendipity, the description of their neurobiological mechanisms made possible to establish the role of norepinephrine, serotonin and, more generally, mono-amines (serotonin, norepinephrine, dopamine) in depression. This discovery, coupled with that of chlorpromazine, led to the appearance of the first real neurobiological theory of a psychiatric disorder, based on an imbalance or depletion of neurotransmitters, and thus to the emergence of biological psychiatry. On the therapeutic level, new MAOIs (phenelzine, tranylcypromine) or new tricyclics (nortriptyline, doxepin, clomipramine among

others) with the same antidepressant effects as the pioneering molecules but each displaying a specific spectrum of psycho-behavioural effects, were described. Then this revolution in biological psychiatry led to the appearance of a new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs). Far from being fortuitous, the discovery of fluoxetine in 1974 by Wong et al. was directly guided by the serotonin theory of depression [10]. Their approach consisted in reproducing as selectively as possible the serotonin reuptake blocking effect induced by several tricyclics, including clomipramine. Although it is debatable whether many SSRIs are "selective" (the noradrenergic action of fluoxetine, for example, is as important as the one of venlafaxine, the leading serotonin and norepinephrine reuptake inhibitor or SNRI [11]), this approach of constructing a molecule on the basis of scientific rationality is also a key stage in the history of psychotropic drugs.

The erosion of the mono-aminergic dogma

The monoaminergic hypothesis of depression has dominated the conception of the pathophysiology of depressive disorders in recent decades. This hypothesis suggests that depression is linked to abnormalities in serotonin, noradrenergic and dopaminergic neurotransmissions. Moreover links between each monoamine imbalance and symptomatic dimensions were proposed. For example, several authors have highlighted the link between anhedonia and dopaminergic transmission. The main hypothesis was a link between depressive symptoms and monoamine depletion. Intensive research on the question in the 1960s and 1970s brought contradictory results and did not allow this hypothesis to be empirically validated (the most robust result, however, being that of lower serotonin levels in the cerebrospinal fluid of patients who died by suicide). It was then suggested that the abnormality could be due to a defect in the expression of monoamine receptors (again, the results were inconclusive), or in the transduction of the signal at the intracellular level. However, a striking gap is present between the weak experimental data supporting the monoamine hypothesis of depression and the fact that most psychotropic drugs used in this disease target one of these three neurotransmitters. This hiatus is also expressed in the development of new antidepressants, with the risk of a circular search. Because of the success of serotonergic antidepressants (and their good tolerance), part of the research has focused on reproducing the effects of these molecules. Thus, the screening of new antidepressant molecules still involves, in animals, to reproduce the effects on serotonergic or noradrenergic transmissions rather than real antidepressant effects modelled by the behaviour of resignation in mice (possibly assessed by swimming time of a mouse in cold water or tail suspension test [12]). This pitfall is also expressed in the tools used to measure the clinical effect of new molecules. Thus, one of the most widely used scales, the MADRS (Montgomery-Åsberg Depression Rating Scale), has been constructed by selecting from a larger depression scale the items most likely to change under serotonergic treatments [13]. By construction, these tests are particularly sensitive to serotonergic interventions and therefore favour the selection of molecules acting via this neurotransmission.

Moreover, the limits of the therapeutic arsenal are obvious. Even if certain psychotherapeutic approaches, particularly cognitive-behavioural approaches, have shown their effectiveness in depression [14], the basic treatment of severe depression is based on antidepressants. However, the therapeutic effect of these molecules is only perceived after 2 to 6 weeks and improvement is slow and progressive, leaving patients in great suffering during this period [15,16]. On the other hand, the remission rate is only 33% after a first well-conducted antidepressant treatment and 67% after four lines of treatment [17]. After the fourth line, the probability of remission to a new line of conventional treatment is less than 10%. Thirty to fifty percents of patients therefore show resistance to drug treatment. These successive failures lead to a chronicization of the depression (lasting more than 24 months), which is known to be a factor of therapeutic resistance. Electroconvulsive therapy (ECT) then remains the reference treatment. However, it appears that new strategies are needed.

Discovery of the antidepressant effects of ketamine

Ketamine is a partial antagonist of the glutamatergic NMDA receptor. It has been used medically since the 1970s, initially for its anaesthetic and sedative properties and later at lower doses in analgesia. The antidepressant and suicidolytic properties of ketamine have been explored since the 2000s. John H. Krystal, last author of the first publication reporting the antidepressant effects of ketamine, indicates that his approach would have been guided by a theoretical perspective [18]. While his group was studying the psychotomimetic effects of ketamine, they had the idea of using it to modulate glutamatergic transmission within the limbic system (albeit in a non-specific way since glutamate is ubiquitous). This first randomized placebo-controlled trial on a small number of patients ($n=9$) demonstrated spectacular and rapid antidepressant effects, within two hours of administration and maximum at 24 hours [19]. Subsequently, many studies have shown the efficacy of intravenous administration of sub-anæsthetic doses of ketamine on depressive symptoms [18,20–23]. Most of the subsequent studies have followed the regimen proposed by Berman et al. in 2000 i.e. administration of a 40-minute intravenous infusion at a dose of 0.5 mg/kg, which is more effective than lower doses (0.1 - 0.4 mg/kg) [24]. One of the strengths of ketamine treatment is its rapid onset of action, with an antidepressant response (50% decrease in depression score) appearing within hours of treatment in more than 50% of patients and within 24 hours in approximately 50-70% of patients [25]. The response is maintained after one week in 35% of patients following a single administration, leading to the development of repeated administration protocols to prolong the response [24]. Indeed, although extremely rapid, the response to ketamine is time limited. The efficacy of ketamine has also been demonstrated for the treatment of bipolar depression [26] and drug-resistant depression [27]. It appears to be effective on all depressive symptoms, including suicidal ideation, classically related to the intensity of moral pain [28]. Studies show a reduction in the suicidal thoughts at 2 hours and 24 hours after infusion even after

controlling for improvement in depressive symptomatology [29]. At a dosage of 0.5 mg/kg iv, plasmatic concentration does not result in loss of consciousness. Common adverse effects during ketamine infusion are increased heart rate and blood pressure as well as perceptual disturbances (perceptual distortion and depersonalization-derealization) [30]. Other adverse effects include anxiety, confusion, dizziness, drowsiness, intense euphoria, nausea and increased muscle tone. All adverse effects of ketamine are transient, with normalization between 5 minutes to 4 hours after the end of the infusion. While there are no studies on the long-term effects of ketamine use in the treatment of depression, data on the repeated use of ketamine in other medical settings (analgesia, anaesthesia), often at higher dosages, or in research settings including patients with schizophrenia, show that adverse effects are limited [31–33].

It should be noted that the S-enantiomer of racemic ketamine, which has a higher affinity for the NMDA receptor than the R-enantiomer, has also shown efficacy in patients resistant to conventional drug therapy [34]. The adjunctive administration of esketamine to oral antidepressant therapy (SSRIs or SNRIs) was first successfully tested in 2018 in a phase 2 placebo-controlled study in 67 patients with resistant depression [35]. Patients were treated twice a week for 2 weeks, then weekly for 3 weeks and then every 2 weeks for a total of 11 weeks. Another phase 2 trial, investigating suicidal ideation and rapid relief of depressive symptoms, was conducted in 2018 in 68 depressed patients with suicidal ideation, demonstrating significant relief of suicidal ideation and depressive symptomatology as early as 4 hours after treatment [36]. A short-term (4-week) phase 3 study in 223 patients with resistant depression confirmed these results [37], which were further supported by a long-term study of the therapeutic potential of esketamine in the prevention of depressive relapse [35]. In this study, a stable response or remission was achieved after an initial phase of bi-weekly administration during two weeks, followed by a consolidation phase of 1 administration per week or every other week for 12 weeks, in 297 of the 455 patients with resistant depression. During the maintenance phase, esketamine reduced the risk of recurrence by 51% in patients in clinical remission (absence of depressive symptoms) and by 70% in patients with a response but no remission (50% reduction in symptoms). The use of esketamine intranasally was approved in 2019 by the FDA for the treatment and prevention of relapse of resistant depression [38] and has recently obtained marketing authorization in France. Here again, the effects of esketamine are rapid, potentially revolutionizing the treatment of depression, when very long hospital stays are usually required to prevent the risk of suicide while waiting for treatment to take effect. Studies on esketamine also provide evidence that it is possible to maintain this strategy over the long term and not just as a transitional treatment.

Which mechanisms?

Glutamatergic transmission, and what else?

The main pharmacological property of ketamine is a non-competitive glutamate antagonist action on a specific type of receptor for this neurotransmitter, the NMDA

(N-methyl-D-aspartate) receptor. Glutamate is the most abundant neurotransmitter in the central nervous system, where it has an excitatory role, i.e. it causes activation of the post-synaptic neuron receiving glutamate. It is involved, among other things, in memory and neuronal plasticity. Two types of ionotropic glutamate receptors, NMDA and AMPA (α -amino-hydroxyl-5-methyl-4-isoxazolepropionate), have been described and have an important role in neuroplasticity. They are both present in the glutamatergic synapse on the post-synaptic neuron. However, NMDA receptors have other extra-synaptic localizations on the pre- and post-synaptic neurons as well as on inhibitory GABAergic interneurons present near the synapse [39]. Intracellular transduction pathways downstream of the AMPA and NMDA receptors have different cellular effects in the post-synaptic neuron. AMPA receptors are channel receptors involved in sodium and potassium ion exchange, they activate rapidly upon reception of glutamate, and lead to activation of intracellular signalling pathways involved in neurogenesis (BDNF, mTOR). The NMDA receptors are activated in a second step, when the AMPA receptors have already caused a first post-synaptic depolarization, and are particularly involved in memorization. They are channel receptors allowing the passage of sodium, potassium and calcium ions. In the basal state, there is a spontaneous current that maintains a weak tonic secretion of glutamate from the pre-synaptic neuron to the post-synaptic NMDA receptors (mEPSC, miniature excitatory post-synaptic current). Tonic stimulation of the post-synaptic NMDA receptor activates the eEF2 kinase (eukaryotic Elongation Factor 2 kinase), which inhibits eEF2, an elongation factor, and then inhibits the synthesis of proteins such as BDNF, a neurotrophic factor [40]. On the other hand, activation of NMDA receptors located outside the synapse will lead to intracellular cascades resulting in an inhibition of mTOR pathway. Finally, stimulation of AMPA receptors will lead to an increase in BDNF, while stimulation of NMDA receptors will tend to inhibit the production of BDNF and a number of proteins secreted in response to this protein. The activation ratio between AMPA receptors and NMDA receptors is therefore particularly crucial for the post-synaptic neuron. Furthermore, if the activation of NMDA receptors is too important, the massive influx of calcium ions has a deleterious, neurotoxic effect on the cell [41]. It is interesting to note that two other actors are essential to understand the modulation of glutamatergic transmission: GABAergic inhibitory neurons, which also possess NMDA receptors, and glial cells, which constitute with neurons the nervous tissue. For example, astrocytes recapture glutamate at the synaptic cleft, allowing the signal to be quickly stopped and the glutamate to be recycled to maintain glutamatergic transmission.

Several studies have shown that, in the context of depression, neuroplasticity is impaired in the anterior cingulate cortex and hippocampus, leading to hypoactivity in these regions and a decrease in glutamatergic transmission at synapses [42]. Administration of ketamine causes an increase in glutamatergic transmission, particularly in the anterior cingulate cortex. This phenomenon is primarily a consequence of the blockade of NMDA receptors located on the GABAergic interneurons. Thus, stopping the stimulation of these interneurons removes the inhibition of glutamatergic neurons and releases glutamate [43]. Since postsynaptic

NMDA receptors are also antagonized by ketamine, the released glutamate preferentially activates postsynaptic AMPA receptors and triggers BDNF synthesis. It is important to note that antagonization of AMPA receptors in mice reverses the antidepressant effect of ketamine. Also in mice, it was shown that, in a context of chronic stress leading to anxiety and depression, the density of dendritic spines, which are the structures carrying the synapses, was lowered. In these mice, 24 hours following ketamine administration, regrowth of dendritic spines was observed, in parallel with a decrease in anxiety-depressive symptoms [44]. Synaptogenesis is therefore strongly stimulated by ketamine and may be involved in its rapid antidepressant effects.

Mu-opioid receptors

In a curious twist of history, one of the possible mechanisms of action of ketamine brings us back to opioid transmission and the mu-opioid receptor. It has been reported that the antidepressant effects of ketamine are annihilated by pre-medication with naltrexone, a competitive antagonist of the mu-opioid receptor [45,46]. This result has been partially replicated in animal models showing that the opioid system would be necessary but not sufficient to explain the antidepressant effects of ketamine [47]. As in humans, mu-opioid receptor blockade antagonized the effects of ketamine, but the effects of direct stimulation of the mu-opioid receptor were not similar to those produced by ketamine, and vice versa. This double dissociation is important since it re-emphasizes, beyond the argument of principle, that the involvement of a neurobiological pathway does not necessarily imply the reproduction of all the effects (side effects or not) classically associated with it [48]. Thus, the involvement of the opioid system does not necessarily imply a risk of addiction or dependence, and the literature on ketamine (and esketamine) is very reassuring on this point, including cases of repeated and prolonged administration. Moreover, since the publication of this result, several teams using ketamine for antidepressant purposes have retrospectively analysed their data and do not seem to replicate (albeit outside the framework of a double-blind trial) the annihilation of antidepressant effects after administration of a mu-opioid receptor antagonist [49,50].

Neuro-inflammation

Alterations in the immune system have been reported in subjects with depression: plasma levels of CRP, IL-6, IL 1 β and TNF- α are increased in these patients compared to the general population [51,52]. In addition, the prevalence of depressive disorders is higher in subjects with autoimmune diseases or chronic inflammatory diseases. Finally, it is recognized that patients treated with IFN- α are at greater risk of developing a depressive episode [53]. Cytokines produced peripherally during an inflammatory or infectious state can cross the blood-brain barrier and affect nervous tissue cells, in particular astrocytes and the resident immune cells of the brain: microglial cells. Cytokines affect the synthesis of neurotransmitters by altering the functioning of astrocytes and the balance between neuroprotective and

neurotoxic substances. For example, interferon activates several enzymes: GTP-cyclohydrolase, responsible for the synthesis of BH4 (tetrahydrobiopterin, an essential cofactor for the synthesis of monoamines); iNOS, nitric oxide synthase; and IDO, indoleamine 2,3-dioxygenase1, a key enzyme responsible for diverting tryptophan metabolism to the kynurene pathway. In a chronic inflammatory context, the prolonged formation of oxygen free radicals leads to a decrease in BH4 and, consequently, monoamine synthesis. On the other hand, activation of IDO leads to an increase in kynurene (KYN) production, which is accompanied by serotonin depletion [54]. Kynurene is then converted into kynurenic acid (KYNA) by astrocytes or into 3-hydroxy-kynurenic acid (3HK) and then into quinolinic acid (QUIN) in activated microglia [55] (Fig. 1).

KYNA has a protective and antioxidant action in the central nervous system and acts as an NMDA receptor antagonist. Conversely, 3HK and QUIN have a neurotoxic action: 3HK acts as a free radical generator and induces cell apoptosis; QUIN is an NMDA receptor agonist, inhibits glutamate reuptake by astrocytes, damages the blood-brain barrier and induces cell apoptosis.

In animal models, the inflammatory state can be induced by injecting low doses of lipopolysaccharide (LPS), a surface component of some bacteria. This inflammatory state is associated with anxiety-depressive symptoms in mice. Several studies [56,57] found an increase in the central concentrations of 3HK and QUIN compared to KYNA. Furthermore, the inactivation of the IDO enzyme prevents anxiety and depression in mice, even in the presence of an inflammatory state. In humans, post-mortem studies in suicidal patients have shown increased concentrations of QUIN in cerebrospinal fluid. Steiner et al. [58] found microglia activation with increased QUIN production in the anterior cingulate cortex in depressed patients. Moreover, anaesthetists have been interested, for several decades, in the immuno-modulatory properties of ketamine. The use of ketamine perioperatively ensures a lower degree of systemic inflammation in patients, with decreased concentrations of the inflammatory cytokines IL-6 and TNF- α [59]. Several in vitro studies have confirmed the anti-inflammatory action of ketamine in the central nervous system through its action on the Toll-like receptors (TLRs) located on the surface of glial cells [60]. More recently, studies have shown that the increase in QUIN was correlated with depressive symptoms in mice; and a ketamine treatment was able to prevent the onset of depression in these animals [61]. In depressed ketamine-responsive patients, increases in KYNA concentrations 24 hours after the first infusion were correlated with improvement in depressive symptoms at the end of treatment [62]. Finally, in a translational approach, it has been shown that microglial cells, which are activated following injection of LPS in mice, show morphological and metabolic changes following ketamine administration, with a decrease in IL6 production and an increase in the KYNA/QUIN ratio. In depressed patients resistant to usual treatments, it has been also shown that a low KYNA/QUIN ratio before treatment with ketamine (possibly indicative of a neuro-inflammatory state) is associated with a lower depression score at the end of the treatment showing a good response to ketamine [63]. All this suggests that the antidepressant action of ketamine certainly involves an antagonism of the NMDA receptor but

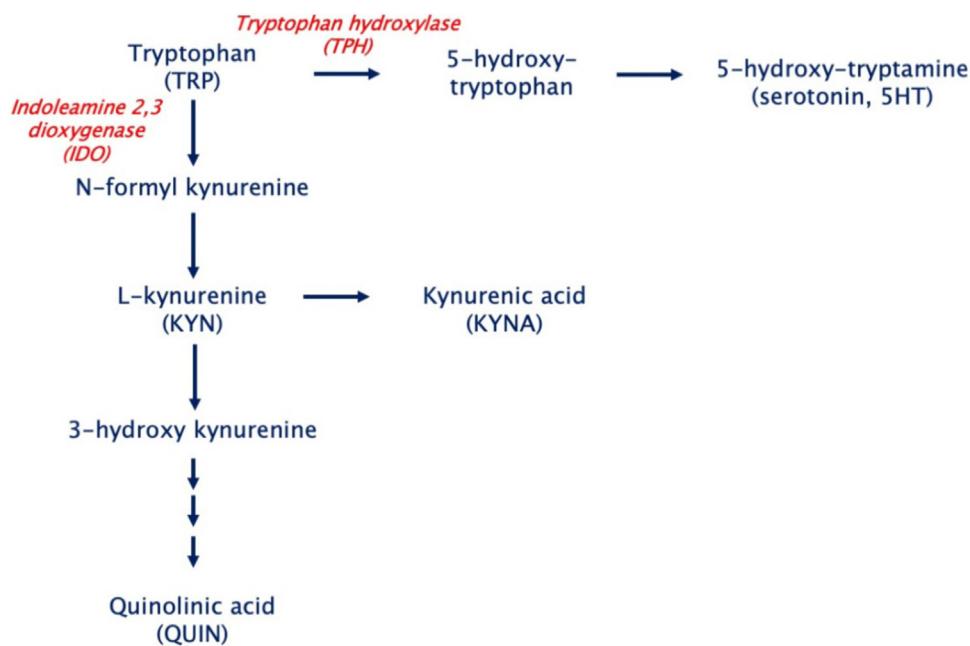


Figure 1 The kynurene pathway.

also a direct action on microglial cells, thus modulating the inflammatory state of the central nervous system.

Cognitive reading?

The psychotomimetic properties of ketamine have been described since its first uses in humans in the 1960s [64]. The administration of ketamine at sub-anaesthetic doses induces, in healthy subjects, alterations in body perception, temporal and spatial disorientation, bizarre impressions and beliefs linked to a misinterpretation of reality (experience of strangeness, impression of being threatened, of being observed, of being guided from the outside) but always accompanied by many doubts, changes in the course of thought and speech alike the diffluence syndrome and, at higher doses, hallucinatory manifestations [65]. This transitory state, perfectly reversible when the infusion is stopped, is clinically closer to the early stages of psychosis (psychotic transition) or even to prodromal signs, than to constituted psychosis, during which delusions are marked by their fixity. Cognitively, ketamine administration seems to induce a crisis of confidence in internal models [66], possibly calling into question the most deeply held ideas in subjects. It has thus been proposed that the phenomenon of "k-hole" (extreme dissociation when approaching the anaesthetic dose) would reproduce certain characteristics of near-death experiences [67]: ineffability, timelessness, the sensation of being dead and dissociated from the body, the sensation of emerging from a tunnel into a bright white light. As these experiences are known to possibly lead to lasting psychological changes in individuals (personality changes, increased self-esteem, increased sense of introspection [68]), some authors had considered the therapeutic use of ketamine for patients frozen in an unshakeable psychological state, such as post-traumatic stress or addiction [69]. The first controlled study evaluating the use of ketamine in the treatment of

depression was conducted a few years later [19]. This hypothetical property of ketamine to induce a psychic state in which the subject may have access to other thought patterns arise from users reporting to have emerged from the "k-hole" with a modified conception of life or of themselves. The experience of taking ketamine could thus be associated with a weakening and recontextualization of previous representations and the exploration of new options. This hypothesis resonates with the particularly striking antidepressant effect of ketamine, whose administration could conceivably lead to a very rapid weakening of the inflexible depressive cognitive representations that characterize this disease.

Conclusion

Ketamine and esketamine, because of their rapid and spectacular effects, even in treatment-resistant forms of depression, are undoubtedly the most promising molecules in the field of depressive disorders since the golden age of psychopharmacology and the discovery of the first antidepressants. Its rapid onset of action could provide rapid relief to patients who currently must endure the excruciating moral pain associated with depression for weeks or even months before they can find relief. The moral or psychic analgesia made possible by these molecules could transform the organisation of care in depression, by allowing more ambulatory treatment, even in the most severe cases. Beyond these considerations, which belong to today's psychotropic drugs more than to those of the future (esketamine already has marketing authorization in France, even if its price has not yet been set), ketamine and esketamine are undoubtedly wonderful triggers for a better understanding of the neurobiological and cognitive pathophysiology of depression. This understanding could allow us to escape serendipity and guide the discovery of other, even more effective molecules. Indeed, just as the discovery of MAOIs

and tricyclics was the milestone to the first neurobiological theory of depression and the importance of monoamines, the appearance of ketamine has put the spotlight on the role of the glutamatergic system or neuro-inflammation in the pathophysiology of this disease. These molecules and the next-generation antidepressants could also lead to a change in the representations of depression, not only in patients but also in relatives and caregivers. All current psychiatrists have learned and experimented that antidepressant effects appear only after several weeks of treatment, making them an inherent property of this psychopharmacological effect. Just as the extrapyramidal effects of neuroleptics have long been considered inseparable from the antipsychotic effects, the slow and progressive effect of antidepressants has led us to construct our representations of depression as a disease that cannot be quickly cured or relieved. For a psychiatrist, a too rapid improvement in depression is often synonymous with a non-expression of the symptoms or a diagnostic error rather than a real improvement. It is even suspicious because it is potentially a precursor of a suicidal act, because of the classically described cathartic effect once the decision made. Some authors have moreover formalized this idea of a progressive unlearning of depressive representations, which would be allowed by treatment [70]. The rapid effect of ketamine, and the discovery of molecules with even more long-lasting effects, could transform these representations, and thus modify the stigmatization that our patients experience on a daily basis.

Disclosure of interest

P.C: declares that he has no competing interest.

A.C.P: conferences: invitations as a speaker for Janssen.

F.V: conferences: invitations as a speaker for Servier Laboratories, Lundbeck SAS, Otsuka Pharmaceutical SAS, LivaNova. Conferences: invitations as auditor (travel and accommodation expenses paid by a company) by Otsuka Pharmaceutical SAS, Lundbeck SAS, Janssen. Occasional interventions: consulting activities for Servier, LivaNova, Otsuka Pharmaceutical SAS, Recordati laboratories.

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